the same medium, they continued to beat, but at independent rates. This was taken to indicate that the stimulus to beat was not transmitted by a humoral agent in the fluid medium surrounding the cells. Furthermore, application of acetylcholine to a small local area of a pulsating network of cells slowed the beat of the entire meshwork, but when the latter was divided into two separate parts and acetylcholine was applied to one part, it slowed the beat in that part but not in the other.

Additional observations indicated that isolated heart cells are of two types: (1) those designated as *leading* cells, which constituted the minority of cells in the culture, appeared as long irregular cells that stained deeply with methylene blue and beat spontaneously; and (2) those termed the *following* cells, which constituted the majority, were smaller, more rounded, stained poorly with methylene blue, and beat only when in contact with leading cells. Similarly, two types of cells have also been recognized in the intact heart: the myocardial cells that constitute the bulk of the heart mass, and a second type of cell found in the specialized tissue concerned with the origination and conduction of the cardiac impulse, i.e. the sinoatrial and atrioventricular nodes and the Purkinje fibre network. It is suggested that the so-called *leading* cells identified in these tissue culture experiments may arise from the nodal and Purkinje tissues, and that the *following* cells may arise from myocardial tissue cells.

Other experiments with tissue culture preparations of cardiac cells indicated that the over-all rate of beating in these cellular aggregates is determined by the fastest beating cells in the meshwork; and although all cells in such a network beat at a common rate, they still retain their own inherent contraction rate which they resume when isolated from the cell mass.

Preparations of individual cells in very dilute cultures constitute an admirable small-scale model of the heart for a variety of physiological, pharmacological, biochemical and metabolic studies. The effect of drugs that influence the heart rate can be measured with great accuracy. Acetylcholine, for example, was found to halt contraction completely when applied in suitable concentration, the period of non-contractility varying with the concentration used. Applications of the cellular enzyme, cholinesterase, which counteracts the effect of acetylcholine, resulted in the resumption of contractile activity. Pre-treatment of the cell with the cholinesterase-inhibitor, eserine, permitted the effect of acetylcholine to persist despite the addition of cholinesterase to the medium, and this action of eserine was, in turn, abolished by ouabain.

Isolated heart cell preparations of this type are also extremely sensitive to agents that block metabolic processes at specific stages. It is known that dinitrophenol (DNP), for example, interferes with the synthesis of adenosine triphosphate (ATP), the substance believed to provide the energy for muscle contraction. Harary and his colleagues found that very low concentrations of DNP inhibited the beating of a single cardiac cell, and that this inhibition could be temporarily eliminated by the addition of ATP to the medium. Thus they concluded that ATP is necessary for cardiac contraction, but recognized the possibility that other energy-supplying mechanisms may be involved as well.

Extension of studies of this nature could conceivably throw new light on the metabolic processes that underlie cardiac activity. Such models also offer an admirable medium for the study of nutritional factors that influence the function, growth and proliferation of cardiac cells.

It must be recognized, of course, that removal of an individual cell from its fellows in the organ and the organism, and placing it in an artificial foreign environment, must affect it profoundly. Cells so treated continue temporarily to function normally because they retain structures and enzymes that were synthesized when they were still in the intact organ. Isolated cardiac cells continue to show, for a time, the typical striations of intact heart cells, synthesize the usual enzymes, even tend to organize themselves into patterns crudely reminiscent of intact cardiac tissue, and they continue to beat. Gradually, however, over a period of days to weeks, they lose their striations, cease to manufacture their specialized enzymes, and in a few weeks cease to beat. Whether these changes reflect a process of de-differentiation to a more primitive embryonic state or a response directed to the new environment, as Harary observes, they present a potentially useful approach to the study of how different types of cells in a developing organism utilize their presumably identical hereditary information in different ways—one of the most important and fundamental problems in biology. The mechanisms governing these responses of a cell to changes in its environment could conceivably provide clues to a better understanding of how the cell manipulates its battery of enzymes to relate to its specific function.

REFERENCES

1. HARARY, I. AND FARLEY, B.: *Science*, **131**: 1674, 1960.
2. HARARY, I.: *Scientific American*, **206**: 141, 1962.

ETIOLOGY OF INTUSSUSCEPTION IN CHILDREN

INTUSSUSCEPTION in children is restricted mainly to those under two years, especially between three and six months. The etiology of intussusception is still not fully understood, but two main theories have been advanced, the dietary and the infective. The dietary theory was postulated partly on the basis of the age distribution of the disease and partly on the basis of a clinical im-

Canad. Med. Ass. J.
Feb. 2, 1963, vol. 88

pression that affected infants were unusually fat and presumably very well fed.

Intussusception is almost three times as frequent in Newcastle-upon-Tyne as in Birmingham and much more frequent than in Edinburgh, Sheffield and Aberdeen. This observation suggested to Knox, Court and Gardner[1] that, in the face of a similar climate and standard of living in these different communities, an explanation for these differences of incidence might be found in differing habits of infant care, such as in feeding methods, rather than from different infection rates. From a retrospective survey of 100 cases of intussusception in children they determined that the weight at birth of these patients was normal. However, children who presented under the age of five months were by then significantly heavier than normal, though this was not true for the older children. It was inferred that the actual rate of growth had been excessive in these patients and that this was probably associated with an excessive food intake. Further evidence for possible dietary factors in the etiology of the disease came from the observation that the flow rates of the nipples used by infants with intussusception were significantly greater than those for the controls. Although it is possible that the rate of build-up of the fluid load (or the concurrent intake of swallowed air or both) is directly causal, these investigators were not able, from their data, to differentiate this from some indirect association. Along with the finding of larger holes in the nipples of the bottles of affected children were the findings that the affected children were more often bottle-fed and that they had their feedings thickened less frequently than controls. In combination, these findings suggest a real difference, in a general if not in a specific sense, between the feeding of infants with intussusception and that of controls.

On the other hand, the widespread assumption of a viral etiology for intussusception in children has received further support in a study by Bell and Steyn[2] of 17 cases of intussusception and of 50 subjects that made up a control group. In each instance an attempt was made to isolate virus from mesenteric lymph nodes removed at laparotomy. The controls were patients submitted to laparotomy for a variety of reasons, the majority being early cases of acute appendicitis. Virus was isolated in 11 of the 17 cases of intussusception and in only five of the 50 control subjects—a statistically significant difference. Furthermore, serological tests indicated a recent or concurrent infection in 10 of the 17 cases of intussusception.

Gardner and colleagues[3] conducted viral and bacteriological investigations in 38 children with intussusception. Infective agents were found to be associated with 80% of the cases. The figure for fecal isolation of adenovirus, 46%, was highly significant when compared with that obtained in a number of control groups. Isolation of the same viruses from throat swabs and lymph nodes, together with the detection of an antibody response, indicated that these isolations represented active and probably recent systemic infections. The main agents isolated were Adenovirus Types 1, 2, 5 and 6 and herpes simplex virus. The conclusion was reached that viruses, particularly adenoviruses, play a causal part in the etiology of intussusception.

It may be that in many cases of intussusception in children both virus infection of the bowel and dietary factors are necessary to give rise to this "mechanical" disease. Before any definite conclusions can be drawn, it will be necessary to confirm both the dietary and viral associations in larger groups of patients and controls. At the same time, the role of miscellaneous factors, such as lumpy foods, purgatives, foreign bodies and trauma, should be investigated.

REFERENCES

1. KNOX, E. G., COURT, S. D. M. AND GARDNER, P. S.: *Brit. Med. J.*, 2: 692, 1962.
2. BELL, T. M. AND STEYN, J. H.: *Ibid.*, 2: 700, 1962.
3. GARDNER, P. S. *et al.*: *Ibid.*, 2: 697, 1962.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

At a meeting of the Berlin Medical Society, recently, Dr. Friedrich Franz Friedmann announced briefly the results of his method of treating tuberculosis by vaccination with living cultures of an avirulent tubercle bacillus. . . . The exact nature and the origin of the cultures, and the details of preparation of the vaccine were not disclosed. Nearly twelve hundred patients, including some two hundred and fifty cases of pulmonary tuberculosis, have been treated during the past few years with one, two, or at most three, injections, generally, it is claimed, with immediate results, such as the healing of long-standing sinuses in bone cases, and the disappearance of symptoms and gradual clearing of physical signs in phthisis, in cases not absolutely hopeless. So assured is Friedmann of the harmlessness of his preparation, that he uses it as a prophylactic, and has treated in this way large numbers of healthy infants, chiefly such as were unusually exposed to tuberculosis infection. This was considered unjustifiable by many doctors present, and called forth vigorous protests. It was pointed out that the injection of living bacilli, even though proved to be avirulent, must always involve risk, owing to the very real possibility of their suddenly acquiring virulence. It seemed to be agreed, however, that a genuine advance had been made, and along the most promising lines; and one can only hope that the great desideratum may, indeed, have been found.—*Canad. Med. Ass. J.*, 3: 54, 1913.